REMARKS

Claims Amendments

Claims 3 and 4 have been canceled.

Claims 1, 5, 7-8 and 20 have been amended.

Claims 23-33 have been added.

Claims 1, 5, 7 and 8, as amended, and new Claim 28 recite "A method of inhibiting TNFα in a human patient, wherein said human patient has a neoplastic disease." The term "*in vivo*" has been deleted. Support is found throughout the specification, for example, at page 3, line 5; page 16, lines 15-26 and page 57, lines 17-27. In addition, support is found in priority application US Serial No. 07/670,827, filed March 18, 1991, at page 3, lines 21-26; page 11, line 13; and page 39, line 20 to page 40, line 4.

Claims 1, 5, 7 and 8, as amended, recite that the antibody or antigen-binding fragment competitively inhibits binding of A2 to TNFα and the claims do not recite cA2. Support is found in the specification, for example, at page 19, line 17 to page 20, line 2 and page 30, lines 8-12. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 12, line 24 to page 13, line 4; page 14, lines 3-9; and page 19, lines 3-10.

New Claim 20 has been amended to recite the method of Claim 19 wherein said single or divided dose is one selected from 0.5, 0.9, 1, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 mg/kg per day on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. Support is found in the specification, for example, at page 60, lines 15-24. In addition, support is found in the specification of priority application US Serial No. 07/943,852, filed September 11, 1992, for example, at page 42, lines 5-18.

New Claim 23 recites "wherein said antibody or antigen-binding fragment comprises a human constant region and a human variable region." New Claim 24 recites "wherein said antibody or antigen-binding fragment comprises at least one human light chain and at least one human heavy chain." New Claim 25 recites "wherein the light chain comprises all antigen-binding regions of the light chain of A2 (ATCC Accession No. PTA-7045)." New Claim 26 recites "wherein the heavy chain comprises all antigen-binding regions of the heavy chain of A2

(ATCC Accession No. PTA-7045)." New Claim 27 recites "wherein the light chain comprises all antigen-binding regions of the light chain of A2 (ATCC Accession No. PTA-7045) and the heavy chain comprises all antigen-binding regions of the heavy chain of A2 (ATCC Accession No. PTA-7045)." Support is found in the specification, for example, at page 25, lines 16-23 and page 27, lines 1-13. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 12, lines 8-25, page 19, lines 14-20; and page 21, lines 11-21.

New Claim 28 further recites "comprises the antigen-binding regions of A2 (ATCC Accession No. PTA-7045)." Support is found in the specification, for example, at page 25, lines 16-23 and page 52, lines 11-12. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at age 19, lines 14-20; and page 38, lines 21-23.

New Claim 29 is directed to "a composition comprising the antibody or antigen-binding fragment of Claim 1, and a pharmaceutically acceptable carrier." Support is found in the specification, for example, at page 61, lines 14-28. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 40, line 22 to page 42, line 9.

New Claim 30 is directed to "the method of Claim 1, wherein the anti-TNF-α antibody or antigen-binding fragment thereof has specificity for a neutralizing epitope of human TNF-α." Support is found in the specification, for example, at page 9, lines 21-24 and page 10, lines 8-15. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 12, lines 18-25.

New Claim 31 is directed to "the method of Claim 1, wherein said Scatchard analysis comprises labeling the anti-TNF-α antibody or antigen-binding fragment thereof and measuring direct binding of ^{125}I labeled anti-TNF-α antibody or antigen-binding fragment thereof to immobilized rhTNFα, and wherein said antibodies are labelled to a specific activity of about 9.7 μCi/μg by the iodogen method." Support is found in the specification, for example, at page 80, line 14 to page 81, line 12. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at Example X, particularly page 67, line 12 to page 68, line 18.

New Claim 32 recites "comprising administering to the human at least one single or divided 0.5 - 50 mg/kg dose." New Claim 33 recites "wherein said single or divided dose is 1 - 10 mg/kg." Support is found in the specification, for example, at page 60, lines 7-24. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 41, lines 3-13.

No new matter has been added. Therefore, entry of the amendments into the application is respectfully requested.

Examiner Interview

Applicants wish to thank the Examiner for meeting with the undersigned to discuss the application, and for providing helpful comments.

Priority

A. Claims 1, 5, 12-14, 16-17, 19-20 and 22

The Examiner indicates that the written support for these claims is not readily apparent either in the pending or priority applications.

As discussed above, Claims 1 and 5 have been amended to recite "A method of inhibiting TNFα in a human patient, wherein said human patient has a neoplastic disease." Claims 12-14, 16-17, 19-20 and 22 depend upon these claims, and, therefore, contain the same limitation. Support is found throughout the specification, for example, at page 16, lines 15-26 and page 57, lines 17-27. In addition, support is found in priority application US Serial No. 07/670,827, filed March 18, 1991, at page 3, lines 21-26; page 19, lines 3-6; and page 39, line 20 to page 40, line 4.

Therefore, the priority application 07/670,827 (filed March 18, 1991) provides sufficient written description for Applicants' claimed methods of "a method of inhibiting TNFα in a human patient, wherein said human patient has a neoplastic disease," and Applicants are entitled to claim the benefit of it. This priority application has been properly referenced on page 1 of the specification in compliance with 35 U.S.C. § 120. Therefore, the priority of all pending claims is March 18, 1991.

As discussed above, Claim 20 is entitled to claim the benefit of priority

application USSN 07/943,852, September 11, 1992.

B. Claims 7-10

The Examiner indicates that it does not appear that the priority applications filed previous to priority application USSN 08/192,093, filed 2/4/94 provide sufficient written description for the sequences recited in Claims 7-10.

Claims 7 and 8 recite "...a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO.:3 and SEQ ID NO.:5...." Claims 9 and 10 recites "...a nucleic acid sequence selected from the group consisting of SEQ ID NO.:2 and SEQ ID NO.:4."

Claims 7-10 are entitled to claim the benefit of priority application USSN application 07/670,827 (filed March 18, 1991). As discussed in the Amendment filed on December 23, 2005, the biological deposit for the A2 antibody (designation c134A) with American Type Culture collection (ATCC) under the Budapest Treaty, was deposited on September 22, 2005.

The Federal Circuit has held that reference in the specification to a deposit in a public depository, which makes its contents accessible to the public, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of section 112. *Enzo Biochem v. Gen-Probe*, 323 F.3d 956, 966 (Fed. Cir. 2002). The *Enzo* court reasoned that a person of skill in the art, reading the accession numbers in the patent specification, can obtain the claimed sequences from the ATCC depository by following the appropriate techniques to excise the nucleotide sequences from the deposited organisms containing those sequences. Thus, the court concluded that "reference in the specification to deposits of nucleotide sequences describe those sequences sufficiently to the public for purposes of meeting the written description requirement." *Id.* at 965-966.

Based on the teachings of the specification, one of ordinary skill in the art would have concluded that Applicants were in possession of the claimed invention. Therefore, the priority application 07/670,827 (filed March 18, 1991) provides sufficient written description for Applicants' claims and Applicants are entitled to claim the benefit of it. This priority application has been properly referenced on page 1 of the specification in compliance with 35 U.S.C. § 120.

Even if the Examiner were to disagree, Claims 7-10 are at least entitled to claim the benefit of priority application USSN 07/853,606, filed March 18, 1992. Priority application USSN 07/853,606 provides sufficient written description and enablement for Claims 7-10 (see, for example, the specification at page 12, lines 20-23; Figures 17A-B; page 24, lines 5-17). Please note that the SEQ ID NO. identifiers were later amended to correct an inadvertent error in the specification to clarify that Figure 17B (renumbered Figure 16B after amendment), is a nucleic acid sequence (SEQ ID NO.: 4) and corresponding amino acid sequence (SEQ ID NO.: 5) of the heavy chain variable region of the cA2 monoclonal antibody (see, for example, page 2 of the Amendment filed in US Serial No.: 08/324,799 on March 14, 1997). The nucleic acid sequence (SEQ ID NO: 2) and corresponding amino acid sequence (SEQ ID NO:3) of the light chain are also disclosed. This application has been properly referenced on page 1 of the specification in compliance with 35 U.S.C. § 120.

Rejection of Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 under 35 U.S.C. § 112, second paragraph

Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite in the recitation of cA2.

In order to further prosecution, Claims 3 and 4 have been canceled and Claims 1 and 5 have been amended to recite that the antibody or antigen-binding fragment competitively inhibits binding of A2 to TNFα and the claims do not recite cA2, thereby rendering the rejection moot. Claims 12-14, 16-17, 19-20 and 22 depend upon these claims, and, therefore, contain the same limitation. Claims 7-10 recite sequences and do not recite cA2 and these claims are definite. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 under 35 U.S.C. § 112, second paragraph

Although the Examiner rejected Claims 1, 3-5, 7-12, 14-15, 21, 23-24 and 26-32, Applicants assume that this is a typographical error, and that Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite in the recitation of 'TNFα-mediated neoplastic disease.'

Applicants respectfully disagree. In order to further prosecution, Claims 3 and 4 have been canceled. Claims 1, 5 and 7-8 have been amended to recite "a method of inhibiting TNFα in a human patient, wherein said human patient has a neoplastic disease." Claims 9-10, 12-14, 16-17, 19-20 and 22 depend upon these claims, and, therefore, contain the same limitation. The claims as amended are definite because the term "neoplastic disease" is a term of general knowledge and a person of ordinary skill in the art would understand the metes and bounds of inhibiting TNFα in a human patient, wherein said human patient has a neoplastic disease.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 under 35 U.S.C. § 112, first paragraph

Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 have been rejected under 35 U.S.C § 112, first paragraph as lacking written description for the phrase 'TNFα-mediated neoplastic disease.'

Applicants respectfully disagree. To further prosecution, Claims 3 and 4 have been canceled. Claims 1, 5 and 7-8 have been amended to recite "a method of inhibiting TNFα in a human patient, wherein said human patient has a neoplastic disease." Claims 9-10, 12-14, 16-17, 19-20 and 22 depend upon these claims, and, therefore, contain the same limitation. As noted above in the section regarding priority, the specifications of both this application and the priority application US Serial No. 07/670,827, filed March 18, 1991, provide sufficient written description for inhibiting TNFα in a human patient, wherein said human patient has a neoplastic disease. The specification discloses that elevated levels of TNF-α are associated with neoplastic disease. Therefore, the specification discloses the inhibition of TNFα in a human, wherein said human has a neoplastic disease by the administration of an anti-TNFα antibody.

The Examiner further states that neither the priority applications nor the instant application provides a sufficient description of a representative number of species to represent the entire genus of 'TNF-α-mediated neoplastic diseases', as currently claimed. As noted above, the claims as amended refer to "neoplastic disease" rather than "TNF-α-mediated neoplastic disease." The term "neoplastic disease" is specifically disclosed in the specification, for example, at page 3, lines 1-5. Additionally, the term "neoplastic disease" is specifically

disclosed in the priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 10, line 22 to page 11, line 4. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 under 35 U.S.C. § 112, first paragraph

Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 have been rejected under 35 U.S.C § 112, first paragraph as lacking enablement. Specifically, the Examiner states that the specification does not teach how to effectively treat any 'TNFα-mediated neoplastic disease' by administering anti-TNFα antibodies.

Applicants have amended Claims 1, 5 and 7-8 to recite "a method of inhibiting TNFα in a human patient, wherein said human patient has a neoplastic disease." Claims 9-10, 12-14, 16-17, 19-20 and 22 are dependent upon these claims, and, therefore, contain the same limitation. The instant specification teaches effective treatment of TNFα-mediated diseases with the claimed antibodies (see the instant specification, for example, Examples XIX-XXV, pages 98-143). Although there is not a specific example in the instant specification directed to inhibiting TNFα in a human, wherein said human has a neoplastic disease, the mechanism of inhibiting TNFα would be the same regardless of the TNFα-mediated disease. Claims 3 and 4 have been canceled.

On page 7 of the Office Action, the Examiner states that "pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be absorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment."

In regard to the Examiner's statement regarding proteolytic inactivation, Applicants note that A2-specific monoclonal antibodies have long half-lives (for example, REMICADE® infliximab has a serum half-life of 9.5 days and still detectable in serum 8 weeks after infusion)

(see Exhibit A, Cornillie *et al.*, "Infliximab Induces Potent Anti-inflammatory and Local Immunomodulatory Activity but no Systemic Immune Suppression in Patients with Crohn's Disease," *Aliment. Pharmacol. Ther., 15*: 463-473, at 463 (2001)). In fact, monoclonal antibodies by their nature have long half-lives. Further, Applicants have canceled claims directed to oral administration and administration via the lungs in order to further prosecution. A2-specific monoclonal anti-TNFα antibodies are generally administered intravenously or subcutaneously. They are not subject to proteolytic degradation, which may occur with oral administration of certain proteins. In regard to the Examiner's statement regarding reaching the target area, Applicants note that the A2-specific antibodies do cross the mucosa as seen in clinical trials with Crohn's disease (see Exhibit A). Exhibit A demonstrates that A2-specific antibodies, such as REMICADE® infliximab, are effective in treating Crohn's disease. Further, in regard to the Examiner's statement regarding suitability of A2-specific antibodies for *in vivo* therapeutic use, Applicants note that A2-specific antibodies, such as REMICADE® infliximab, have been administered successfully to patients with various TNFα-mediated diseases for over a decade. A2-specific antibodies have proven to be safe and effective.

Thus, undue experimentation would not be required to practice the invention. As discussed above, Applicants' disclosure provides considerable direction and guidance on how to practice the invention and presents working examples. Based on the content of the disclosure, and what was known in the art at the time of the invention, one of ordinary skill in the art would not be subject to undue experimentation to make and use the invention.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 under 35 U.S.C. § 112, first paragraph

Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 have been rejected under 35 U.S.C § 112, first paragraph as lacking enablement for cA2.

As discussed above, Claims 1 and 5 have been amended to recite that the antibody or antigen-binding fragment competitively inhibits binding of A2 to TNFα and the claims do not recite cA2, thereby rendering the rejection moot. Claims 16-17, 19-20 and 22 depend upon these

claims, and, therefore, contain the same limitation. Claims 3 and 4 have been cancelled. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 have been rejected under 35 U.S.C. § 103(a)

Claims 1, 3-5, 7-10, 12-14, 16-17, 19-20 and 22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Verhoef *et al.*, *Leukemia, 6*:1268-1272 (1992) in view of Le *et al.* (WO 92/16553).

As discussed above, while Applicants disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to further prosecution, as discussed above, Claims 3 and 4 have been canceled and Claims 1, 5 and 7-8 have been amended to recite "a method of inhibiting TNFα in a human patient, wherein said human patient has a neoplastic disease", thereby rendering the rejection moot. As discussed above, support for these claim amendments is found in the specification, for example, at page 57, lines 17-27. In addition, support is found in priority application US Serial No. 07/670,827, filed March 18, 1991, at page 3, lines 21-26 and page 39, line 20 to page 40, line 4. Claims 9, 10, 12-14, 16, 17, 19, 20 and 22 depend upon these claims, and, therefore, contain the same limitation. As discussed above, Claim 20 is entitled to is entitled to claim the benefit of priority application USSN 07/943,852, September 11, 1992.

As discussed above, the claims, as amended, are entitled to priority to 07/670,827 (filed March 18, 1991). Therefore, neither Le *et al.* (published October 1, 1992) nor Verhoef *et al.* (December 12, 1992) are prior art. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Deirdre E. Sanders

Deirdre E. Sanders
Registration No. 42,122
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Dated: September 18, 2006